APPROVED PACKAGE INSERT

SCHEDULING STATUS S 4

PROPRIETARY NAMES AND DOSAGE FORM

BERIGLOBIN® P 2 ml Solution for Injection for subcutaneous or intramuscular administration

BERIGLOBIN® P 5 ml Solution for Injection for subcutaneous or intramuscular administration

COMPOSITION

1 ml contains:

Human protein	160,0 mg
thereof immunoglobulins G at least	95 %

Distribution of IgG subclasses:

IgG_1 ca. 61 %

IgG_2 ca. 28 %

IgG_3 ca. 5 %

IgG_4 ca. 6 %

IgA max. 1,7 mg/ml

antibodies to hepatitis A virus at least 100 IU

Other ingredients:

Aminoacetic acid (glycine), sodium chloride, HCl or NaOH (in small amounts for pH adjustment), water for injections.

PHARMACOLOGICAL CLASSIFICATION

A 30.1 Biologicals – Antibodies

PHARMACOLOGICAL ACTION

Pharmacodynamic properties:

Normal human immunoglobulin contains mainly immunoglobulin G (IgG) having a broad spectrum of antibodies against various infectious agents.

BERIGLOBIN P contains the immunoglobulin G antibodies present in the healthy population. It is usually prepared from pooled plasma of at least 1 000 donors. It has a distribution of immunoglobulin G subclasses closely proportional to that in native human plasma. Adequate doses of this medicinal product may restore abnormally low immunoglobulin G levels to the normal range.

Pharmacokinetic properties:

With subcutaneous administration of human normal immunoglobulin, peak levels are achieved in the recipient's circulation after approximately 2 days.

Data from a clinical study (n=60) show that trough levels of approximately 8 to 9 g/l (n=53) in the plasma can be maintained by weekly doses between 0,05 and 0,15 g (0,3 to 0,9 ml) Beriglobin P per kg body weight. This is commensurate to a monthly cumulative dosage of 0,2 to 0,6 g per kg body weight.

With intramuscular administration BERIGLOBIN P is bioavailable in the recipient's circulation after a delay of approximately 2 to 3 days.

IgG and IgG-complexes are broken down in cells of the reticuloendothelial system.

INDICATIONS

Replacement therapy in adults and children in primary immunodeficiency syndromes such as:

- Congenital agammaglobulinaemia and hypogammaglobulinaemia, including therapy induced.
- Common variable immunodeficiency.
- Severe combined immunodeficiency.
- IgG subclass deficiencies with recurrent infections.

Replacement therapy in myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections.

Hepatitis A prophylaxis:

- In travelers who present less than 2 weeks before possible exposure, preferably in combination with vaccination.

For long-term hepatitis A prophylaxis, active immunization is recommended.

- In persons exposed less than 2 weeks previously.

Therapy of radiogenic mucositis

CONTRA-INDICATIONS

Hypersensitivity to any of the components of the product.

Beriglobin P must not be administered intramuscularly in cases of disorders of haemostasis.

WARNINGS

Do not inject intravascularly!

If BERIGLOBIN P is accidentally administered into a blood vessel, patients could develop shock or thromboembolic events. When administering intramuscularly it is recommended to ensure by aspiration that no vessel has been penetrated.

The recommended infusion rate stated under ‘DOSAGE AND DIRECTIONS FOR USE” should be adhered to.

INTERACTIONS

Live attenuated virus vaccines:

Immunoglobulin administration may impair for a period of at least 6 weeks and up to 3 months the efficacy of live attenuated virus vaccines such as measles, rubella, mumps, and varicella vaccines. After administration of BERIGLOBIN P, an interval of at least 3 months should elapse before vaccination with live attenuated virus vaccines.

In the case of measles, this impairment may persist for up to 1 year. Therefore patients receiving measles vaccine should have their antibody status checked.

Interference with serological testing:

It has to be considered that when serological test results are interpreted, the transitory rise of passively transferred antibodies after immunoglobulin injection may result in positive test results. Passive transmission of antibodies to erythrocyte antigens, e.g., A, B and D, may interfere with some serological tests for red cell allo-antibodies (e.g. Coombs test), reticulocyte count and haptoglobin.

PREGNANCY AND LACTATION

There are no controlled clinical trials on the use in human pregnancy. Therefore, the administration of this medicinal product to pregnant women or breast-feeding mothers should be carefully considered.

Long lasting clinical experience with immunoglobulins suggests that no harmful effects on the course of pregnancy or on the fetus and the neonate are to be expected.

DOSAGE AND DIRECTIONS FOR USE

Dosage:

The dosage and intervals of infusion are dependent on the indication.

Replacement therapy:

The product should be administered via the subcutaneous route.

The dosage may need to be individualised for each patient dependent on the pharmacokinetic and clinical response. The following dosage regimens are given as a guideline.

The dosage regimen using the subcutaneous route should achieve a sustained level of IgG. A loading dose of at least 0,2 to 0,5 g/kg (1,3 to 3,1 ml/kg) bodyweight - divided over several days with a maximal daily dose of 0,1 to 0,15 g/kg body weight and as indicated by the treating doctor - may be required. After steady state IgG levels have been attained, maintenance doses are administered at repeated intervals, ideally weekly, to reach a cumulative monthly dose of about 0,4 to 0,8 g/kg (2,5 to 5,0 ml/kg) bodyweight.

Trough levels should be measured in order to adjust the dose and dosage interval.

Hepatitis A prophylaxis:

The product is to be administered via the intramuscular route.

- Short-term prophylaxis in travellers who present less than 2 weeks before possible exposure:

For stays in endemic areas of less than 3 months a dose of 0,003 to 0,004 g/kg (0,02 ml/kg) bodyweight is recommended to be administered intramuscularly. BERIGLOBIN P can be given in combination with hepatitis A vaccine, but at different sites of the body.

- Hepatitis A prophylaxis in persons exposed less than 2 weeks previously:
  0,003 to 0,004 g/kg (0,02 ml/kg) bodyweight administered intramuscularly.

Therapy of radiogenic mucositis:

The product is to be administered via the intramuscular route.

Initially 10 ml (1600 mg), after 2 days 5 ml (800 mg) and after a further 2 days again 5 ml (800 mg).

The treatment can be repeated as often as necessary.

Administration:

BERIGLOBIN P is a ready-for use solution and should be administered at body temperature.

BERIGLOBIN P is a clear solution. The colour can vary from colourless to pale-yellow up to light brown. Do not use solutions which are cloudy or contain residues (deposits/particles).

The product must be inspected visually prior to administration and should not be used if there is any variation of physical appearance.

Method of administration:

Depending on the indication, BERIGLOBIN P should be administered via the subcutaneous or intramuscular route.

Subcutaneous administration:

Subcutaneous infusion should be initiated and monitored by a physician experienced in the treatment of immunodeficiencies and in the guidance of patients for home treatment. The patient will be instructed in the use of a syringe driver, infusion techniques, the keeping of a treatment diary and measures to be taken in case of severe adverse events. The recommended infusion rate is 22 ml/hour. In a clinical study with 53 patients evaluated, during the training phase under supervision of a physician, the infusion rate was increased from initially 10 ml to 22 ml/hour.

Do not inject intravascularly! Note that there is an increased risk of inadvertent intravascular injection in patients who have repeatedly received intramuscular injections.

The product should preferably be administered in the abdominal wall, thigh and/or buttocks. No more than 15 ml should be injected into a single site. Doses over 15 ml should be divided and injected into 2 or more sites.

Intramuscular administration:

Intramuscular injection must be given by a doctor or nurse.

BERIGLOBIN P should preferably be administered ventrogluteally with the patient lying down. If larger doses are required, it is advisable to administer them in divided fractions. This applies in the case of doses above 2 ml for persons up to 20 kg bodyweight and doses above 5 ml for persons above 20 kg bodyweight.

Do not inject intravascularly! Note that there is an increased risk of inadvertent intravascular injection in patients who have repeatedly received intramuscular injections.

Any unused product or waste material should be disposed of in accordance with local requirements.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS

In a clinical study with subcutaneous administration in 60 patients the following undesirable effects have been reported.

The following standard categories of frequency are used:

Very common	≥ 1/10
Common	≥ 1/100 and < 1/10
Uncommon	≥ 1/1 000 and < 1/100
Rare	≥ 1/10 000 and < 1/1,000
Very rare	< 1/10 000 (including reported single cases)

Body as a whole – general disorders:

Rare: In single cases: Generalised reactions such as chills, fever, headache, malaise, moderate back pain, syncope, dizziness, rash, bronchospasm. Allergic reactions including fall in blood pressure.

Application site disorders:

Very common: Swelling, soreness, redness, induration, local heat, itching, bruising or rash.
The frequency declined very rapidly within the first ten infusions, when patients became used to the subcutaneous form of treatment. (In study patients who were treated with subcutaneous immunoglobulin for years before the trial, injection site reactions were not reported.)
Adverse reactions reported from post marketing surveillance are similar to the reactions which have also been observed during the clinical trials. In addition, the following have also been reported during post marketing surveillance:

Cardiovascular disorders, general:

Uncommon: Cardiovascular reactions particularly if the product has been inadvertently injected intravascularly.

Vascular (extracardiac) disorders:

Uncommon: Vascular disorders associated with subcutaneous substitution therapy: There are reports from patients being treated subcutaneously with high doses of immunoglobulins for substitution therapy (e.g. primary immunodeficiency syndrome) of arterial and venous thromboembolic events including myocardial infarction, stroke, deep venous thrombosis and pulmonary embolism.

Body as a whole – general disorders:

Uncommon: Allergic/anaphylactic reactions including dyspnoea, cutaneous reactions, in isolated cases reaching as far as anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration. Generalised reactions such as nausea, vomiting, arthralgia.

Special precautions:

Do not inject intravascularly! If BERIGLOBIN P is accidentally administered into a blood vessel, patients could develop shock. When administering intramuscularly, it is recommended to ensure by aspiration that no vessel has been penetrated.
The recommended infusion rate stated under “DOSAGE AND DIRECTIONS FOR USE” should be adhered to.
Patients should be closely monitored and carefully observed for any adverse event throughout the infusion period.

Certain adverse reactions may occur more frequently in patients who receive human normal immunoglobulin for the first time or, in rare cases, when the product is switched or when treatment has been paused for more than eight weeks.

True hypersensitivity reactions are rare. They can occur in the very rare cases of IgA deficiency with anti-IgA antibodie, and these patients should be treated with caution.

Rarely, BERIGLOBIN P can induce a fall in blood pressure with anaphylactic reaction, even in patients who had tolerated previous treatment with normal human immunoglobulin.

Potential complications can often be avoided by ensuring that

- patients are not sensitive to BERIGLOBIN P by first injecting the product slowly (see also "DOSAGE AND DIRECTIONS FOR USE");
- patients are carefully monitored for any symptoms throughout the infusion period.

In particular, patients should be monitored during the first infusion and for the first hour thereafter, in order to detect potential adverse reactions in the following situations:

- patients naïve to human normal immunoglobulin,
- patients switched from an alternative product, or
- when there has been a long interval since the previous infusion.

All other patients should be observed for at least 20 minutes after administration.

On suspicion of an allergic or anaphylactic reaction the administration has to be discontinued immediately. In case of shock the current medical standards for shock treatment have to be applied.

Thromboembolic events associated with subcutaneous substitution therapy:

The subcutaneous use of high doses of immunoglobulins for substitution therapy (e.g. primary immunodeficiency syndrome) have been associated with arterial and venous thromboembolic events including myocardial infarction, stroke, deep venous thrombosis and pulmonary embolism. Caution should be exercised in prescribing BERIGLOBIN P for subcutaneous substitution therapy in such patients with pre-existing risk factors for thrombotic events (such as advanced age, hypertension, diabetes mellitus and a history of vascular disease or thrombotic episodes, patients with acquired or inherited thrombophilic disorders, patients with prolonged periods of immobilisation, severely hypovolemic patients, patients with diseases which increase blood viscosity). These patients should be informed about first symptoms of thromboembolic events including shortness of breath, pain and swelling of a limb, focal neurological deficits and chest pain

and should be advised to contact their physician immediately upon onset of symptoms. Such patients should be sufficiently hydrated before use of BERIGLOBIN P.

Important information about some special excipients of Beriglobin P:

This medicine contains up to 110 mg sodium per dose (body weight 75 kg) if the maximal daily dose (11,25 g = 70,3 ml) is applied. To be taken into consideration in patients on a controlled sodium diet.

Virus safety:

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV, and for the non-enveloped viruses HAV and parvovirus B19.

There is reassuring clinical experience regarding the lack of hepatitis A or parvovirus B19 transmission with immunoglobulins and it is also assumed that the antibody content makes an important contribution to the virus safety.

In the interest of patients, it is strongly recommended that every time that BERIGLOBIN P is administered to them, the name and batch number of the product is recorded in order to maintain a link between the patient and the batch of the product.

Effects on ability to drive and use machines:

Beriglobin P should not affect your ability to drive and use machines

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

There are no known symptoms of overdosage.

IDENTIFICATION

Solution for injection for subcutaneous or intramuscular administration.

BERIGLOBIN P is a clear solution. The colour can vary from colourless to pale-yellow up to light brown during shelf life.

PRESENTATION

BERIGLOBIN® P 2 ml: A single dose 2 ml clear glass ampoule packed into a carton.

BERIGLOBIN® P 2 ml: A single dose 2 ml pre-filled syringe packed into a carton.

BERIGLOBIN® P 5 ml: A single dose 5 ml clear glass ampoule packed into a carton.

BERIGLOBIN® P 5 ml: A single dose 5 ml pre-filled syringe packed into a carton.

STORAGE INSTRUCTIONS

Store in a refrigerator at 5 ºC ± 3 ºC in the outer carton in order to protect from light. Do not freeze!

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS

BERIGLOBIN® P 2 ml:

T/30.2/608

11/30.2/0037 (Namibia)

BERIGLOBIN® P 5 ml:

T/30.2/609

11/30.2/0038 (Namibia)

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Actor Pharma (Pty) Ltd [1]

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Gauteng, South Africa

On behalf of: CSL Behring GmbH, 35041 Marburg, Germany

DATE OF PUBLICATION OF THIS PACKAGE INSERT

The date on the registration certificate of BERIGLOBIN P: 09 September 1992

The date of the most recently revised package insert as approved by Council: 15 October 2012

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[1] Company Registration number: 2008/008787/07